

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/047824 A1

(51) International Patent Classification⁷: **A61K 31/155**,
31/444, 31/42, 31/18, 31/381, 31/407, 31/415, 45/06,
A61P 29/00, 19/02, 11/06, 11/00, 17/00, 17/06, 35/04,
1/04, 1/00, 25/00, 9/10

(74) Common Representative: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**; Binger Strasse 173, 55216 Ingelheim (DE).

(21) International Application Number:
PCT/EP2003/012874

(22) International Filing Date:
18 November 2003 (18.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02026223.4 26 November 2002 (26.11.2002) EP

(71) Applicant (for all designated States except US):
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BIRKE, Franz** [DE/DE]; Albrecht-Dürer-Strasse 21, 55218 Ingelheim (DE). **JENNEWEIN, Hans, Michael** [DE/DE]; Idsteiner Strasse 14, 65193 Wiesbaden (DE).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

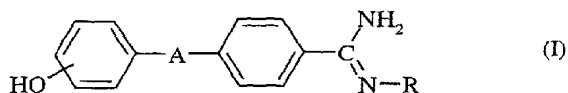
(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A LTB₄ ANTAGONIST AND A COX-2 INHIBITOR OR A COMBINED COX1/2 INHIBITOR



(57) Abstract: The invention relates to a pharmaceutical formulation comprising a LTB₄ antagonist having a hydroxy and a benzamide group or a tautomer, a pharmaceutically acceptable salt or solvate thereof, in particular a compound of formula (I), wherein R and A are as defined in the claims, or a tautomer, a pharmaceutically acceptable salt or solvate thereof (1) and at least one cyclooxygenase-2 inhibitor, a combined cox1/2 inhibitor or a pharmaceutically acceptable salt or solvate thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.



WO 2004/047824 A1

PHARMACEUTICAL COMPOSITION COMPRISING A LTB₄ ANTAGONIST
AND A COX-2 INHIBITOR OR A COMBINED COX1/2 INHIBITOR

5

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The invention relates to a pharmaceutical composition comprising certain oral available, LTB₄ antagonist, which contains a hydroxy and a benzamidine group, or a tautomer, a
10 pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and at least one cyclooxygenase-2 inhibitor or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

15

2. BACKGROUND INFORMATION

The US patent US 6,172,096 discloses a method of reducing recipient acute or chronic rejection of transplanted cells or organs, and for treatment of autoimmune diseases, hypersensitivity reactions of the acute or delayed type, allergic disorders, granulomas, meningitis, and septic
20 shock by administering a cyclooxygenase-2 inhibitor and a leukotriene B₄ (LTB₄) receptor antagonist.

LTB₄ antagonists which contain a hydroxy and benzamidine group are compounds with pharmacologically valuable properties. Such LTB₄ antagonists may provide great therapeutic
25 benefit, for example, in the treatment of arthritis, asthma, chronic obstructive lung diseases, psoriasis, ulcerative colitis, Alzheimer's disease, shock, reperfusion damage/ischaemia, cystic fibrosis, atherosclerosis and multiple sclerosis.

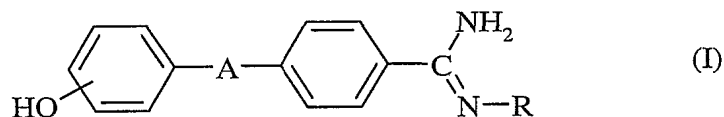
Such compounds are known e.g. from International Patent Applications WO 96/02497, WO
30 97/21670, WO 98/11062, WO 98/11119, WO 01/25186 and PCT/EP01/00262 .

However, none of these prior art references indicates that the combination of a cyclooxygenase-2 inhibitor and a LTB₄ antagonists having a hydroxy and a benzamidine group will show a synergistic effect, in particular for the treatment of rheumatic arthritis.

- 5 It has been demonstrated that arachidonic acid produced a dermal inflammation when applied topically (Carter et al, 5-Lipoxygenase inhibitory activity of zileuton. J Pharmacol Exp Ther 256, 929-937 (1990)). This inflammation is rich in neutrophils and consequently myeloperoxidase (MPO), a neutrophil marker enzyme, can be used as a quantitative index for cell infiltration. The mouse ear is especially suited to serve as a model of dermal inflammation induced by various
 10 agents like arachidonic acid which is known to be metabolized to several inflammatory mediators i.e. prostaglandines and LTB₄. Accordingly neither an LTB₄ antagonist nor an NSAID alone are supposed to fully counteract this kind of inflammation. Therefore this model seems to be useful to test the efficacy of a NSAID-LTB₄ antagonist combination .
- 15 It has now be found surprisingly that a pharmaceutical formulation comprising a cyclooxygenase-2 inhibitor and a LTB₄ antagonists having a hydroxy, preferably a phenolic hydroxy group and a benzamidine group shows a synergistic effect, in particular for the treatment of rheumatic arthritis.

20 BRIEF SUMMARY OF THE INVENTION

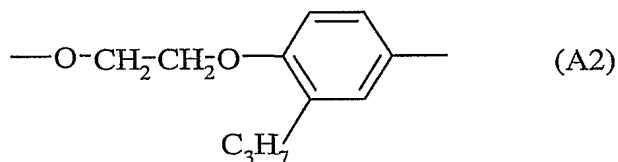
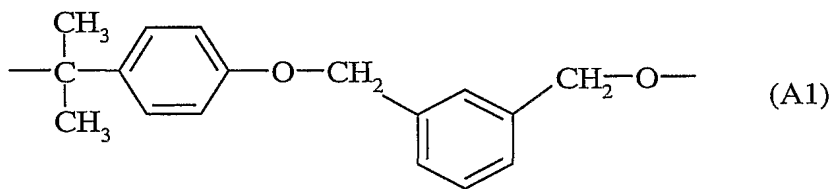
The invention relates to a pharmaceutical composition comprising a LTB₄ antagonists having a hydroxy and a benzamidine group, preferably a compound of formula (I)



wherein

- 25 R represents a hydrogen atom or a group of formula -CO₂-R', in which R' represents a C₁₋₆ alkyl, an optionally substituted phenyl group or an optionally substituted benzyl group, wherein the optional substituents are selected from halogen atoms C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, nitro; C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy groups, and
 A is a group selected from the formulae (A1) and (A2):

- 3 -



or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and

- 5 at least one cyclooxygenase-2 inhibitor or combined cox1/cox2 inhibitor or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

- 10 R preferably represents H or $-\text{CO}_2\text{-C}_2\text{H}_5$.

Another aspect of the present invention is a method for the prevention or treatment of a disease or disorder selected from the group consisting of arthritis, including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, asthma, hay fever, atopic dermatitis, rhinitis, bronchitis, COPD and cystic fibrosis, psoriasis, scleroderma, morbus bechterew, sarcoidosis, tumor metastasis, morbus crohn, colitis ulcerosa, IBD, multiple sclerosis, arteriosclerosis, arteritis, myocardial infarction, stroke, coronary heart disease which method comprises administration of effective amounts of a LTB_4 antagonist having a hydroxy and a benzamidine group, preferably a compound of formula (I) (1) and a cyclooxygenase-2 or combined cox1/cox2 inhibitor (2) to a patient in need thereof in a combined form, or separately or separately and sequentially wherein the sequential administration is close in time or remote in time.

Furthermore, the invention relates to the use of a LTB_4 antagonist having a hydroxy and a benzamidine group, preferably a compound of formula (I) (1) and a cyclooxygenase-2 inhibitor (2) in a combined form, or separately or separately and sequentially, wherein the sequential administration is close in time or remote in time, for the manufacture of a medicamentation for

the prevention or treatment of disease or disorder selected from the group consisting of arthritis, including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, asthma, bronchitis, COPD and cystic fibrosis.

Finally, the invention relates to pharmaceutical kit comprising at least two separate unit dosage forms (A) and (B):

(A) one of which comprises a composition containing a LTB_4 antagonist having a hydroxy and a benzamidine group, preferably a compound of formula (I), a tautomer thereof or a pharmaceutically acceptable salt thereof (1), and optionally a pharmaceutically acceptable carrier;

(B) one of which comprises a composition containing one or more cyclooxygenase-2 inhibitors or combined cox1/ 2 inhibitors (2), and optionally a pharmaceutically acceptable carrier.

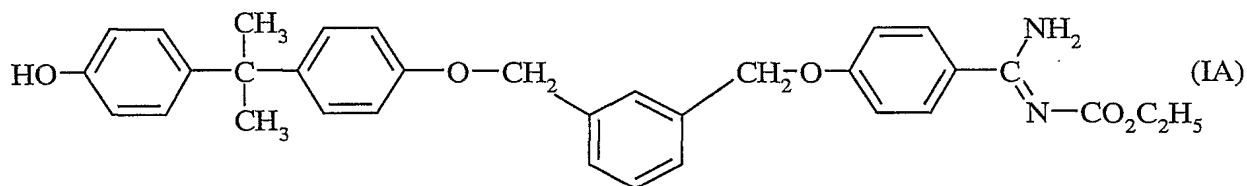
DETAILED DESCRIPTION OF THE INVENTION

The term " LTB_4 antagonists which contain a hydroxy and benzamidine group" embraces compounds which selectively inhibit the leukotriene B_4 receptor and corresponding products thereof. They have preferably a "rod-like" structure of up to 5, preferably 3 or 4 phenylene moieties, which are connected to each other by linking groups selected from single bonds; straight chained or branched C_{1-4} -alkylenediyl, -O- C_{1-4} -alkylenediyl, C_{1-4} -alkylenediyl-O- and -O- C_{1-4} -alkylenediyl-O-. One of the said phenylene moieties, preferably a terminal one, carries a amidine group ($-C(=NH)-NH_2$), wherein the imino hydrogen atom may also be replaced by a capping group which enhances the bioavailability of the compound and is cleaved of under physiological conditions. Preferably one of the othe phenylene moieties, most preferably the other terminal one, carries a phenolic hydroxy group.

The term "capping group" preferably represents a group of formula $-CO_2R'$, wherein R' has the meaning given hereinabove.

The term " C_{1-6} alkyl" embraces straight chained and branched alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl *n*-propyl, *i*-propyl, *n*-butyl, 2-butyl, *n*-pentyl and *n*-hexyl.

Preferred is a pharmaceutical composition, wherein the active principle essentially consists of a compound of formula (I), in particular formula (IA)

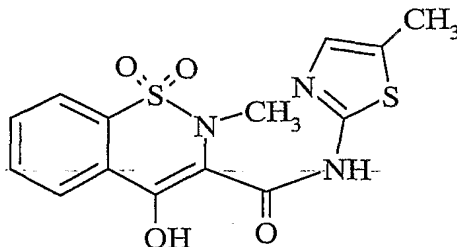


(1) and one cyclooxygenase-2 inhibitor or combined cox1/cox2 inhibitor.

5

The term "cyclooxygenase-2 inhibitor" embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, or which are combined cyclooxygenase-1 and cyclooxygenase-2 inhibitors.

Preferred are the cyclooxygenase-2 inhibitor or combined cox1/coxII inhibitor selected from the group consisting of celecoxib, Dupont Dup 697, etodolac, etoricoxib, flosulide, meloxicam, nimesulide, parecoxib, rofecoxib, Taisho NS-398 and valdecoxib, in particular meloxicam of formula



or a pharmaceutically acceptable salt thereof.

15

The phrase "combination therapy" (or "co-therapy"), in defining use of a cyclooxygenase-2 inhibitor agent and a leukotriene B₄ receptor antagonist agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination. The phrase also is intended to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

20

The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in severity and the

frequency of disease incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

The active substance of formula I may be present in the formulation according to the invention in the form of a physiologically acceptable acid addition salt. By physiologically acceptable acid addition salts are meant, according to the invention, pharmaceutically acceptable salts which are selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid. Mixtures of the above acids may also be used to prepare the salts.

According to the invention, the preferred salts of formula I are selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate and methanesulphonate. The salts selected from among the hydrochloride, hydrobromide and fumarate are particularly preferred. The active substance may optionally be in the form of a hydrate. Preferably, according to the invention, the compound of formula I is added to the tablet in the form of the free base and in the anhydrous form.

The pharmaceutical formulation according to the present invention is as a rule suitable for oral, intravascular, intraperitoneal, subcutaneous, intramuscular or topical administration, in particular oral administration.

The present invention preferably relates to a tablet containing a compound of formula I and a cyclooxygenase-2 inhibitor or a combined cox1/cox2 inhibitor which contains at least one pharmacologically acceptable excipient, and optionally at least one wetting agent.

The term "wetting agent" as used hereinbefore and hereinafter denotes an excipient which lowers the surface tension of water or other liquids so that they can penetrate into the surfaces of the tablets according to the invention and soak through them, displacing the air, thereby wetting them. The substances used as wetting agents are usually interface-active surfactants. These surfactants are amphiphilic (bifunctional) compounds with at least one hydrophobic and one hydrophilic part of the molecule. The hydrophobic group is usually a hydrocarbon chain, if possible a straight chain, with eight to 22 carbon atoms. Particular surfactants may also have (dimethyl)-siloxane chains or perfluorinated hydrocarbon chains as the hydrophobic part of the molecule. The hydrophilic group is either a negatively or positively charged (hydratable) or a

neutral polar head group. Of the surfactants, anionic surfactants, particularly the long-chain alkylsulphates, especially sodium laurylsulphate and alkylbenzenesulphonates are preferred.

Within the scope of the present invention carbohydrates such as lactose or mannose, particularly
5 finely divided lactose or sugar alcohols such as mannitol, sorbitol or xylitol, particularly mannitol, are of particular importance as excipients. These excipients have proved particularly advantageous in the formulation according to the invention. In a preferred aspect, therefore, the present invention relates to a tablet containing at least one compound of formula I, which contains, in addition to the active substance and the wetting agent, lactose, particularly finely
10 divided lactose, more preferably lactose monohydrate or mannitol as excipient.

The tablet according to the invention may also contain compounds capable of acting as binders.

The term "binder" used hereinbefore and hereinafter denotes excipients which are suitable for
15 binding other components to one another. Preferred binders according to the invention are selected from among:

powdered cellulose, microcrystalline cellulose, sorbitol, starch, polyvinylpyrrolidone (povidone), copolymers of vinylpyrrolidone with other vinyl derivatives (copovidone), cellulose derivatives, particularly methylhydroxypropylcellulose, e.g. Methocel A 15.LV, and mixtures of these
20 compounds. The preferred binders are powdered cellulose, particularly microcrystalline cellulose and/or copovidone. Most preferred is a mixture of microcrystalline cellulose and a copolymer of vinylpyrrolidone and vinyl acetate, namely copovidone VA 64, the ratio of vinylpyrrolidone and vinyl acetate being about 3:2 (m/m). As a rule the tablet according to the invention has a weight ratio of microcrystalline cellulose to copovidone VA 64 of 20:1 to 1:1, preferably 15:1 to 2:1,
25 particularly about 10:1 to 3:1. Thanks to this particularly preferred binder combination of microcrystalline cellulose and copovidone, tablets are obtained having a high bioavailability of the compounds of formula I.

The tablet according to the invention may also contain disintegrants in addition to the above
30 mentioned ingredients. Within the scope of the present invention these disintegrants may optionally also be known as breakdown agents. These are preferably selected, according to the invention, from among sodium starch glycolate, crosslinked polyvinylpyrrolidone (crospovidone), croscarmellose sodium salt (sodium salt of cellulose carboxymethyl ether,

crosslinked), sodium-carboxymethylcellulose, dried maize starch and mixtures thereof. Within the scope of the present invention it is particularly preferred to use sodium starch glycolate, crospovidone and, preferably, the sodium salt of crospovidone or croscarmellose.

- 5 The tablet according to the invention may also contain flow agents or flow regulators and also lubricants, as additional ingredients. These include, within the scope of the present invention, for example, silicon dioxide, talc, stearic acid, sodium stearyl fumarate, magnesium stearate and glycerol tribehenate. According to the invention magnesium stearate is preferably used.
- 10 In addition, the tablet according to the invention may contain one or more synthetic or natural, pharmaceutically acceptable dyes or colourings, preferably indigo carmine. If the abovementioned colourings are used the amount by weight thereof based on the total mass of the tablet according to the invention is 0.01 to 0.5 wt. %.
- 15 The active ingredients (1) and (2) are as a rule applied in a ratio, in which the resulting combination exhibits a synergistic effect. The term "synergistic effect" as used herein relates to an effect, which is higher than one could expect from the additive effects of each single active ingredient.
- 20 Accordingly, the pharmaceutical formulation according to the present invention exhibits as a rule (1) and (2) in synergistically effective amounts of, preferably a weight ratio of (1) to (2), which ranges from 50 : 1 to 1 : 300, preferably from 8:1 to 1:80, in particular 1:1 to 1:40, most preferably 1:5 to 1:30.
- 25 The pharmaceutical formulation according to the present invention are preferably administered in a single application dose containing 1 to 10,000 milligrams, preferably 5 to 1000 mg of the combined active ingredients (1) and (2). Most preferred is a formulation comprising about 10 mg meloxicam and up to 300 mg of formula IA.
- 30 The Examples that follow serve to illustrate some formulations according to the invention. They are intended solely as possible procedures described by way of example, without restricting the invention to their content.

Example 1

Ingredients	
(01)	compound IA, jet-ground
(02)	meloxicam
(03)	microcrystalline cellulose
(04)	mannitol
(05)	croscarmellose sodium
(06)	sodium laurylsulphate
(07)	indigo carmine (11-14 %)
(08)	magnesium stearate

mg/tablet
1,000
10,000
15,000
52,250
1,500
0,050
0,075
1,125
81,000

The direct compression comprises producing a premix of ingredients (01), (02), (06), (07) and some of (04) with an intensive mixer. The premix is screened and mixed with ingredients (03), (05) and the remainder of (04) in a gravity mixer. After the mixture has been screened again, ingredient (08) is added.

Example 2**2.1 Animals**

Female albino mice (Han:NMRI) obtained from Interfauna and weighing about 20-25 g were used. The animals were provided with standardised pellet diet (Altromin 8013) and had tap water freely available. The animals were accommodated in a climatized room with a 12 hours light/dark cycle and kept in groups.

2.2 Chemical substances***Compound of formula IA:***

Carbamic acid, [[4-[[3-[[4-[1-(4-hydroxyphenyl)-1-methylethyl]-phenoxy]methyl]phenyl]methoxy]phenyl]iminomethyl]-, ethyl ester was prepared as described in US 6,417,382.

Meloxicam was provided by Boehringer Ingelheim Pharma KG

Arachidonic acid was purchased from Sigma (A9798) and dissolved 1:10 in acetone.

5 2.3 Study Design

The compound of formula IA and meloxicam were administered orally (0.2 ml / 10 g bw) 30 min. before arachidonic acid challenge. Meloxicam was given twice: one dose 16 hours and the second dose 30 minutes before challenge. For every day there was a concurrent control. Then number of animals per group was 7. The study compounds were suspended in 1% methylcellulose (Tylose MH 300, Fluka, CH-9470 Buchs). The experiment was run in five groups. Details are given in Table 1. Every group contained one control, two doses of meloxicam, two doses of (IA), and one dose of the combination of the two compounds.

Table 1

Treatment	N	Dose m/kg p.o.)	Dose m/kg p.o.)	Dose m/kg p.o.)	Dose m/kg p.o.)	Dose m/kg p.o.)
		Group 1	Group 2	Group 3	Group 4	Group 5
Control- (Tylose)	7					
Meloxicam	7	1	2	4	8	16
Meloxicam	7	2	4	8	16	32
(IA)	7	0.05	0.1	0.2	0.4	0.8
(IA)	7	0.1	0.2	0.4	0.8	1.6
Meloxicam plus (IA)	7	1 0.05	2 0.1	4 0.2	8 0.4	16 0.8

2.4 Experimental Procedure

Mice were lightly anesthetized by ether and 1 mg arachidonic acid (10 µl) was applied to each side of the left ear. The right ear remained untreated, acetone alone did not cause any late response. The animals were sacrificed by ether 6 hours later, and a biopsy

(diameter 8 mm) was punched out from both ears to assess an increase of neutrophils in the left ear compared with the right ear. Tissue samples were homogenized in 1 ml 0.5% HTAB (Hexadecyl-trimethyl-ammonium-bromide; Sigma H-5882; solved in 0.05 M phosphate buffer, pH 6.0) using a tissue homogenizer (IKA-Ultraturrax T5; Janke & Kunkel, Staufen/Breisgau) at 30000 RPM for 15 seconds. After centrifugation (16000 G, 5 min) the supernatants were frozen until processing for myeloperoxidase (MPO). Determination in the supernatants for MPO, a neutrophil marker enzyme, served as a quantitative index for the neutrophil accumulation.

MPO was determined spectrophotometrically at 450 nm using a micro plate version of the method of Bradley (1982) and a micro plate reader (V_{\max} ; Molecular Devices, Palo Alto) suitable for kinetic measurements and expressed as mean optical density per minute.

2.5 Statistical Evaluation

For each individual the response myeloperoxidase activity (MPO) in optical density per minute (oD/min) was measured.

Based on these results the following statistical analyses were done:

- Comparison of control groups
- Comparison of Control vs. Treatments separately for each group
- Comparison of high vs. low dose for both treatments separately for each group
- Comparison of combined treatment vs. high doses separately for each group
- Comparison of combined treatment vs. other treatments in group 5

For the comparisons the nonparametric statistical methods Kruskal-Wallis-One-Way-ANOVA and the Wilcoxon-Two-Sample-Test (2sided) have been used. For the first and last comparisons also Bonferroni-Holm adjusted p-values have been calculated.

The calculations and statistical analysis were done with the NPAR1WAY procedure of the SAS software program (SAS Institute Inc., Cary, North Carolina) version 8.2. (IA) and meloxicam both inhibited arachidonic acid induced ear inflammation in mice. Details of statistical analysis are shown in tables 2 to 4.

Table 2 Difference between treatment and control

Group	Treatment Compound / dose [mg/kg]	p-value	p-value (adj)
1	Meloxicam / 1	1.0000	n.s.
	Meloxicam / 2	0.2502	n.s.
	(IA) / 0.05	0.7983	n.s.
	(IA) / 0.	0.7491	n.s.
	Meloxicam / 1+(IA) / 0.05	0.8983	n.s.
2	Meloxicam / 2	0.0152	0.0304
	Meloxicam / 4	0.1252	0.1252
	(IA) / 0.1	0.0060	0.0240
	(IA) / 0.2	0.0073	0.0219
	Meloxicam / 2 + (IA) / 0.1	0.0022	0.0110
3	Meloxicam / 4	0.0736	0.0736
	Meloxicam / 8	0.0049	0.0147
	(IA) / 0.2	0.0073	0.0146
	(IA) / 0.4	0.0033	0.0165
	Meloxicam / 4 + (IA) / 0.2	0.0033	0.0165
4	Meloxicam / 8	0.3067	n.s.
	Meloxicam / 16	0.7015	n.s.
	(IA) / 0.4	0.0553	0.1659
	(IA) / 0.8	0.0106	0.0424
	Meloxicam / 8 + (IA) / 0.4	0.0022	0.0110
5	Meloxicam / 16	0.1599	n.s.
	Meloxicam / 32	0.2246	n.s.
	(IA) / 0.8	0.0049	0.0196
	(IA) / 1.6	0.0072	0.0216
	Meloxicam / 16 + (IA) / 0.8	0.0017	0.0085

Table 35 Comparisons High/Low Treatment and High Treatment vs Combination

Group	Low Dose [mg/kg]	High Dose [mg/kg]	p-value
1	Meloxicam / 1	Meloxicam / 2	0.3067
	(IA) / 0.05	(IA) / 0.1	0.8983
2	Meloxicam / 2	Meloxicam / 4	0.7983
	(IA) / 0.1	(IA) / 0.2	0.7983
3	Meloxicam / 4	Meloxicam / 8	0.0474
	(IA) / 0.2	(IA) / 0.4	0.5229
4	Meloxicam / 8	Meloxicam / 16	0.7983
	(IA) / 0.4	(IA) / 0.8	0.9490
5	Meloxicam / 16	Meloxicam / 32	0.4320
	(IA) / 0.8	(IA) / 1.6	0.7012

Group	High Dose [mg/kg]	Combination [mg/kg]	p-value
1	Meloxicam / 2	Meloxicam / 1 + (IA) / 0.05	0.1792
	(IA) / 0.1	Meloxicam / 1 + (IA) / 0.05	0.8983
2	Meloxicam / 4	Meloxicam / 2 + (IA) / 0.1	0.0033
	(IA) / 0.2	Meloxicam / 2 + (IA) / 0.1	0.0348
3	Meloxicam / 8	Meloxicam / 4 + (IA) / 0.2	1.0000
	(IA) / 0.4	Meloxicam / 4 + (IA) / 0.2	0.3067
4	Meloxicam / 16	Meloxicam / 8 + (IA) / 0.4	0.0033
	(IA) / 0.8	Meloxicam / 8 + (IA) / 0.4	0.0215
5	Meloxicam / 32	Meloxicam / 16 + (IA) / 0.8	0.0026
	(IA) / 1.6	Meloxicam / 16 + (IA) / 0.8	0.0086

Table 4Comparisons Combination vs Others for Group 5

Comparison vs combined (Group5)	p-value	p-value (adj)
Control	0.0017	0.0085
Meloxicam / 16	0.0032	0.0096
Meloxicam / 32	0.0026	0.0104
(IA) / 0,8	0.0090	0.0090
(IA) / 1,6	0.0086	0.0172

5

The arachidonic acid induced mouse ear inflammation test is indicative for pathological processes where neutrophils are involved (see also introduction). It shed light especially on the chemoattractant part of the arachidonic acid cascade induced neutrophil activation. The results indicate that (IA) and Meloxicam are effective orally and consequently may target important parts of this inflammation..

10

With respect to the combination of both compounds, there are two criteria which must be fulfilled to prove a super-additive efficacy (potentiation).

- i.) the maximal achievable effect of the combination must be bigger than the maximal achievable effect of the single compound.
- ii.) the effect of the combination should be bigger than the effect which can be expected from the dose response curve of the single compounds

15

The first criterion is experimentally tested by using supra-maximum doses of the single compounds and compare these with the achievable maximal effect of the combination. This may be difficult when the compounds under investigation produce a 100% inhibition itself. Therefore the model of arachidonic acid induced mouse ear inflammation was chosen, because NSAIDs and LTB₄ antagonists demonstrate very shallow dose response curves and a 100% inhibitory effect is hardly possible. As shown in the present experiments of group5 the supra-maximum doses of meloxicam (16 and 32 mg/kg p.o.) and (IA) (0.8 and 1.6 mg/kg p.o.) achieved maximum inhibitory effects of 37% and 66% respectively, whereas the combination (meloxicam

20

25

16 mg/kg p.o., (IA) 0.8mg/kg p.o.) achieved a maximum inhibition of 96%. This difference was statistically significant and consequently proves a super-additive effect according to criterion i.).

5 The second criterion can be tested by doubling the doses of the single compounds and compare the effect of the higher doses of the single compounds with the effect of the combination of the lower doses of the single compounds. In group 1 all doses were too low to achieve any effect and consequently the results of this experiment cannot be used either to accept or reject the hypothesis of potentiation. The same holds true for the experiments in group 3. Although the combination achieved the highest inhibition, the difference to the inhibition reached with the
10 highest doses of the single compounds were not statistically significant, because the single compounds alone caused already high inhibition values. However the experiments performed in group 2, 4, and 5 clearly show that the combination was significantly more effective than the higher doses of the single compounds thus proving a super-additive efficacy according to criterion i.i.

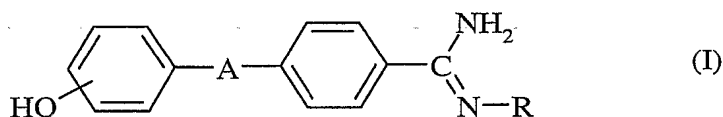
15

It is concluded that the combination of the non steroidal anti inflammatory drug meloxicam with the LTB₄ antagonist (IA) strongly inhibits arachidonic acid induced mouse ear inflammation after oral administration in an super-additive way

CLAIMS:

1. A pharmaceutical composition comprising a LTB₄ antagonist having a hydroxy and a benzamidine group, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and at least one cyclooxygenase-2 inhibitor or combined cox1/coxII inhibitor or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

2. A pharmaceutical composition according to claim 1 wherein said LTB₄ antagonist is a compound of formula (I)

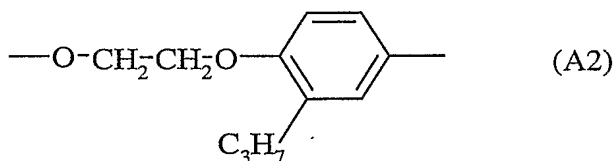
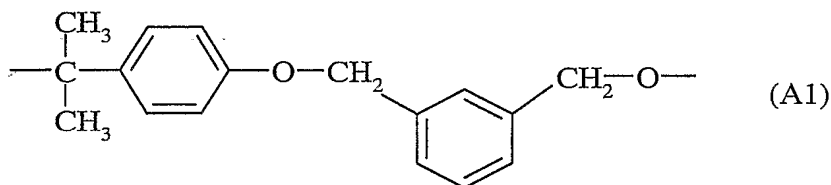


wherein

R represents a hydrogen atom or a group of formula -CO₂-R', in which R' represents a C₁₋₆ alkyl, an optionally substituted phenyl or an optionally substituted benzyl group, wherein the optional substituents are selected from halogen atoms C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, nitro; C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy groups, and

15

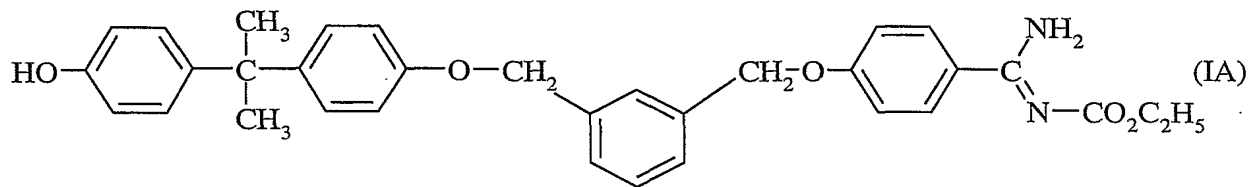
A is a group selected from the formulae (A1) and (A2):



or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1).

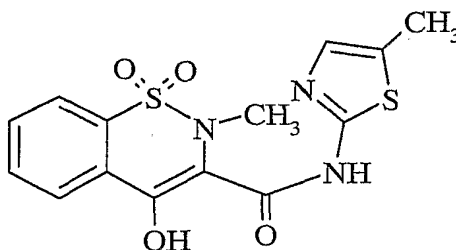
20

3. A pharmaceutical composition according to claim 1 or 2 consisting essentially of the compound of formula (IA)



(1) and one cyclooxygenase-2 inhibitor or combined cox1/coxII inhibitor selected from the group consisting of celecoxib, Dupont Dup 697, etodolac, etoricoxib, flosulide, meloxicam, nimesulide, parecoxib, rofecoxib, Taisho NS-398 and valdecoxib or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient.

4. A pharmaceutical formulation according to one of claims claim 1 to 3 comprising the compound of formula (IA) (1) and meloxicam of formula



or a pharmaceutically acceptable salt thereof (2), and a pharmaceutically acceptable carrier or excipient.

5. A pharmaceutical formulation according to any of claims 1 to 4 which is suitable for oral, intravascular, intraperitoneal, subcutaneous, intramuscular or topical administration.

6. A pharmaceutical formulation according to any of claims 1 to 5 wherein the weight ratio of (1) to (2) ranges from 50:1 to 1 : 300, preferably from 8:1 to 1:80.

7. A pharmaceutical formulation according to any of claims 1 to 6 wherein a single application dose contains 1 to 10,000 milligrams, preferably 10 to 2,000 mg of the combined active ingredients (1) and (2).

8. A pharmaceutical formulation according to any of claims 1 to 7 wherein the pharmaceutically acceptable carrier or excipient is a carbohydrate.

9. A method for the prevention or treatment of a disease or disorder selected from the group consisting of arthritis, including rheumatoid arthritis, spondyloarthropathies, gouty

arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, asthma, hay fever, atopic dermatitis, rhinitis, bronchitis, COPD and cystic fibrosis, psoriasis, sclerodermia, morbus bechterew, sarcoidosis, tumor metastasis, morbus crohn, colitis ulcerosa, IBD, multiple sclerosis, arteriosclerosis, arteritis, myocardial infarction, stroke, coronary heart disease which
5 method comprises administration of effective amounts of a LTB₄ antagonist having a hydroxy and a benzamidine group or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and a cyclooxygenase-2 or combined cox1/coxII inhibitor (2) to a patient in need thereof in a combined form, or separately or separately and sequentially wherein the sequential administration is close in time or remote in time.

10 10. A method according to claim 9 for the prevention or treatment of rheumatoid arthritis, atopic dermatitis and coronary heart disease.

11. Use of a LTB₄ antagonist having a hydroxy and a benzamidine group, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and a cyclooxygenase-2 inhibitor or combined cox1/2 inhibitor (2) in a combined
15 form, or separately or separately and sequentially, wherein the sequential administration is close in time or remote in time, for the manufacture of a medicament for the prevention or treatment of disease or disorder selected from the group consisting of arthritis, including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, asthma, bronchitis, COPD and cystic fibrosis.

20 12. Use according to claim 11 for the manufacture of a medicament for the prevention or treatment of rheumatoid arthritis, atopic dermatitis and coronary heart disease.

13. A pharmaceutical kit comprising at least two separate unit dosage forms (A) and (B):

(A) one of which comprises a composition containing LTB₄ antagonist having a hydroxy
25 and a benzamidine group or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and optionally a pharmaceutically acceptable carrier;

(B) one of which comprises a composition containing one or more cyclooxygenase-2 inhibitors or combined cox1/2 inhibitor, and optionally a pharmaceutically acceptable
30 carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12874

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/155 A61K31/444 A61K31/42 A61K31/18 A61K31/381
A61K31/407 A61K31/415 A61K45/06 A61P29/00 A61P19/02
A61P11/06 A61P11/00 A61P17/00 A61P17/06 A61P35/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/107276 A1 (ANDERSON GARY D ET AL) 8 August 2002 (2002-08-08)	1,4-13
Y	page 1, paragraph 2 page 2, paragraph 15 -page 3, paragraph 31 page 8, paragraph 162 - paragraph 163 page 15, paragraph 202 page 16, paragraph 204 page 16, paragraph 210 claims 1,2,5,9-12,14,17-20 --- -/--	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 2004

Date of mailing of the international search report

10/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cielen, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/12874

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P1/04 A61P1/00 A61P25/00 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 172 096 B1 (ANDERSON GARY ET AL) 9 January 2001 (2001-01-09) cited in the application	1,4-13
Y	column 4, line 52 - column 6, line 64 column 7, line 35 - line 41 column 8, line 58 - column 9, line 16 column 29, line 5 - line 17 column 29, line 33 - line 41 column 30, line 45 - line 52 claims 1-3,6 --- -/--	1-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 2004

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cielen, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/12874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/21670 A (BOEHRINGER INGELHEIM KG ;ANDERSKEWITZ RALF (DE); SCHROMM KURT (DE)) 19 June 1997 (1997-06-19) cited in the application page 14, paragraph 2 - paragraph 4 page 15, paragraph 6 -page 16, paragraph 3 examples CMPDS1,5 claims 1,9-12 ---	1,2,4-13
Y	WO 98/11062 A (ANDERSKEWITZ RALF ;BOEHRINGER INGELHEIM PHARMA (DE); BIRKE FRANZ () 19 March 1998 (1998-03-19) cited in the application page 4, paragraph 3 - paragraph 6 page 6, paragraph 1 - paragraph 3 examples CMPDS3,9,24,28,42,45,59 claims 1,20,21 ---	1,2,4-13
Y	BIRKE, F. W. ET AL: "In vitro and in vivo pharmacological characterization of BIIL 284, a nove and potent leukotriene B4 receptor antagonist" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (2001), 297(1), 458-466 , XP001079480 abstract page 458, column 2, paragraph 2 -page 459, column 1, paragraph 1 page 464, column 1, paragraph 2 -column 2, paragraph 1 page 464, column 2, paragraph 3 -page 465, column 1, paragraph 1 page 465, column 1, paragraph 3 page 465, column 2, paragraph 1 -page 466, column 1, paragraph 1 ---	1-13
Y	BARNES P.J.: "Future advances in COPD therapy." RESPIRATION, (2001) 68/5 (441-448). , XP001084651 table 1 page 442, column 2, paragraph 5 -page 443, column 1, paragraph 1 ---	1-9,11, 13
Y	US 2002/119193 A1 (PAGLIERO ARTHUR J ET AL) 29 August 2002 (2002-08-29) page 5, paragraph 47 - paragraph 48 page 5, paragraph 57 -page 6, paragraph 65 page 6, paragraphs 67,69,71 --- -/--	1-13

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	<p>WO 03/007922 A (BOEHRINGER INGELHEIM PHARMA ;BECKER ROBERT (DE); BOCK THOMAS (DE);) 30 January 2003 (2003-01-30) page 1, line 1 -page 3, line 12 page 4, line 10 -page 5, line 10 page 6, line 24 -page 7, line 2 claims 1,2,5,18,19 -----</p>	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/12874

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 2 and 5-13 relate to compounds defined by reference to a desirable characteristic or property, namely "a LTB₄ antagonist having a hydroxy and a benzamidine group" and "at least one cyclooxygenase-2 inhibitor or combined cox1/coxII inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Moreover, present claims 1-3 and 5-13 relate to compounds which actually are not well-defined. The use of the definition "or physiologically functional derivative thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the LTB₄ antagonists of formulae (I) and (IA), mentioned in claims 2-4 or their tautomers, pharmaceutically acceptable salts or solvates in combination with the COX-2 inhibitors or combined COX1/COXII inhibitors specifically mentioned in claims 3 and 4 or their pharmaceutically acceptable salts or solvates.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/12874

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002107276	A1	08-08-2002	US 6342510 B1	29-01-2002
			AU 6269496 A	09-01-1997
			CA 2224563 A1	27-12-1996
			EP 0833664 A1	08-04-1998
			JP 11507669 T	06-07-1999
			WO 9641645 A1	27-12-1996
US 6172096	B1	09-01-2001	US 6617345 B1	09-09-2003
			AU 2250097 A	02-09-1997
			CA 2246356 A1	21-08-1997
			EP 0880362 A1	02-12-1998
			JP 2000505445 T	09-05-2000
			WO 9729775 A1	21-08-1997
WO 9721670	A	19-06-1997	DE 19546452 A1	19-06-1997
			AT 263144 T	15-04-2004
			AU 716473 B2	24-02-2000
			AU 1369997 A	03-07-1997
			BG 64020 B1	31-10-2003
			BG 102395 A	29-01-1999
			BR 9611949 A	30-03-1999
			CA 2234611 A1	19-06-1997
			CZ 9801836 A3	11-11-1998
			EE 9800145 A	15-10-1998
			WO 9721670 A1	19-06-1997
			EP 1015421 A1	05-07-2000
			HR 960583 A1	28-02-1998
			HU 9903733 A2	28-03-2000
			JP 2000502333 T	29-02-2000
			NO 982708 A	12-06-1998
			NZ 325235 A	28-01-2000
			PL 327171 A1	23-11-1998
			RU 2184726 C2	10-07-2002
			SK 77098 A3	04-11-1998
			TR 9801039 T2	21-08-1998
			TW 438746 B	07-06-2001
			US 6127423 A	03-10-2000
			ZA 9610460 A	10-06-1998
WO 9811062	A	19-03-1998	DE 19636689 A1	12-03-1998
			AT 224363 T	15-10-2002
			AU 727900 B2	04-01-2001
			AU 4383897 A	02-04-1998
			BG 63938 B1	31-07-2003
			BG 103219 A	29-10-1999
			BR 9712816 A	23-11-1999
			CA 2262566 A1	19-03-1998
			CN 1230174 A , B	29-09-1999
			CZ 9900822 A3	15-09-1999
			DE 59708278 D1	24-10-2002
			DK 929516 T3	13-01-2003
			EA 3245 B1	27-02-2003
			EE 9900086 A	15-10-1999
			WO 9811062 A1	19-03-1998
			EP 1203764 A1	08-05-2002
			EP 0929516 A1	21-07-1999
			ES 2184131 T3	01-04-2003
			HK 1020564 A1	18-07-2003

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811062	A	HU 9904367 A2	28-05-2000
		JP 2001504087 T	27-03-2001
		KR 2000036005 A	26-06-2000
		NO 991131 A	09-03-1999
		NZ 334895 A	29-09-2000
		PL 332136 A1	30-08-1999
		PT 929516 T	31-01-2003
		SI 929516 T1	30-04-2003
		SK 29699 A3	13-03-2000
		TR 9900501 T2	21-07-1999
		TW 378200 B	01-01-2000
		US 6197824 B1	06-03-2001
		US 6265612 B1	24-07-2001
		ZA 9708045 A	10-03-1998
US 2002119193	A1	29-08-2002	NONE
WO 03007922	A	30-01-2003	
		DE 10206241 A1	30-01-2003
		CA 2452357 A1	30-01-2003
		WO 03007922 A2	30-01-2003
		EP 1408943 A2	21-04-2004
		US 2003119901 A1	26-06-2003